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by M. Popovskiy

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MEDICINES BUILT INTO MOLECULES

/Following is a translation of an article written by M. Popovskiy in Znaniye-Sila (Knowledge Is Power), No. 4, Moscow, 1959, pages 42-43./

Last year, in issue No. 5 of our journal, we discussed the various "occupations" of substances with large molecules, including the "therapeutic" polymers created in the Moscow laboratory of Professor M. F. Shostakovskiy.

This time we will acquaint you with the works of Leningrad scientists, who are also putting chemistry at the service of medicine.

Polymers Instead of Blood

Recently, in one of the popular journals, an interesting illustration attracted my attention. The artist had depicted all those parts of the human organism which modern chemistry of plastics can replace by artificial "parts." On the background of a human silhouette were portrayed plastic teeth, joints, an artificial esophagus, prosthetic arms, legs, eyes, parts of the cranium and even heart valves. Legends to the figure indicated that modern medicine employs several scores of varied kind of plastic prostheses for the most diversified cases of surgical replacement.

I observed, however, that missing in this large list was a chemical substitute of one exceedingly important human tissue. I speak of blood substitutes.

For several years the scientists of various countries, including researchers in the Soviet Union, have been working with success in creating preparations able to temporarily replace human blood.

"Blood is quite a special juice!" said one of the heroes of Goethe's "Faust." And in fact, a full-value replacement of this red fluid which runs in our vessels seemed, heretofore, conceivable in one case only: if in its place is poured the donor blood taken from another person.

But the ever-increasing demands for blood substitutes has compelled biologists, chemists and doctors to combine their efforts for the purpose of creating a substance which might, even though partially, approximate genuine blood.

The first salt-containing solutions, as they were called, appeared as early as last century. Notwithstanding their considerable imperfection, these solutions gained fairly wide prevalence. In the years of the First World War they were injected into the vessels of wounded men who had lost much blood. The salt solutions, however, "depart" from the vessels fairly swiftly.

The doctors demanded higher quality preparations from biologists and chemists. In the quest of blood substitutes, the biologists turned to natural substances, the chemists to synthetic.

Microorganisms which colonize products containing sugar have long been known. Some of these microscopic fungi convert sugar into a peculiar mucus. These fungi were for a long time considered to be only pests: they spoiled products in confection factories, during breweries and in wine cellars.

But then bacteriologists investigated the viscous mass which brewers and confectioners threw away as waste. It was found to represent highly-molecular substances which in structure (not composition) resembled the liquid part of blood. Such natural blood substitutes were, under the name of "dextrans" put to use in the West. In Leningrad we created another organic blood substitute also derived by means of microbes. "Synkol," as it is called, is now being used in clinical practice.

The chemists took another route. Their purpose was to create artificially a preparation with high molecular weight, similar to blood proteins. The German chemist Reppe synthesized one of the first such artificial blood substitutes. His preparation, polyvinyl-pyrrolidone (PVP in abbreviated form) which has immense molecular weight -- 14 to 15 thousand -- possessed valuable qualities. It was soluble in water. Moreover, the large molecules of this substance could not pass through the vessel walls as readily as the saline solutions passed out. They remained longer in the vascular channel and thereby helped the wounded or sick person's organism to recover its strength. The PVP preparation also entered medical practice.

The synthetic blood substitutes did not, of course, accomplish the main purpose of blood -- they did not carry oxygen from the lungs to the organism's various tissues. But for the gravely wounded person, it also happens to be

important merely to fill the vessels with fluid in order to maintain the heart's work and gain time until the organism itself restores genuine blood. These synthetic blood substitutes were also not depicted by the artist in the illustration that interested me. Such preparations are now attracting the serious attention of chemists and doctors.

In the 1950s Soviet Chemists -- including Prof. Sergey Nikolayevich Ushakov, honored scientist, and corresponding member of the Academy of Sciences USSR -- turned to the synthesis of PVP. A great expert in the chemistry of plastics, Prof. Ushakov, the founder and first director of the Academy of Science USSR's Institute of High-molecular-weight Compounds, has organized 14 new industries in our country. The fifteenth was to have been, as he planned, the production of synthetic blood substitutes.

The manufacture of polyvinyl-pyrrolidone after the Reppe method, however, required very complex equipment. The Soviet scientists decided to simplify production, and in this they succeeded. Tested in various institutes and clinics, the Soviet PVP was given a pass to life. One more valuable preparation was added to the arsenal of blood substitutes.

It would seem that a period might be put after this. And Prof. Ushakov himself thought that after having laid the foundations of the new industry, he, a chemist, would leave the field of medicine. But things turned out differently. The medical ideas took hold of the scientist and led him to a new extremely interesting find.

The Organism Against Medicines

Once in winter, I fell ill after a long trip. My temperature rose, it became hard to breathe, an overpowering weakness developed.

"You have pneumonia," said the doctor, "I will have to prescribe penicillin." And with a smile: "Collect your courage. You will get the antibiotic for five days."

The sense of this sympathetic smile became clear to me after the very first visit of the nurse. The penicillin injection is rather painful and the nurse appeared morning and evening.

"Can the injections be less frequent," I asked the doctor in a half-whisper. "Just once a day, perhaps?"

"Alas, impossible as yet."

"Why?"

It turns out that a successful struggle against the microbes, the causative agent of pneumonia, is possible only in case a constant and sufficiently high concentration

of the medicine is created in the patient's blood. But penicillin just "departs" from the organism too swiftly. The need also arises, therefore, of replenishing the quantity of it in the blood twice a day.

Penicillin is not the only preparation whose stay in the human body is limited to an extremely short time. Among the anti-tubercular medicines, paraaminosalicylic acid of PASK for shorthas become widely known in recent years. Inasmuch as the organism very rapidly frees itself from this medicine as well, the patient has to take it in large doses, reaching 20 grams per day. In consequence, the tuberculosis patient is compelled during treatment to swallow as much as two kilograms of medicine.

A multitude of such examples could be cited. All of them indicate one and the same thing. Our organism gets rid of the majority of medical preparations too swiftly. Scientists have for a long time been searching for substances capable of retaining medicine in the patient's body. Some of these "prolongators," as they are called, have been found. It is, however, possible to use them only for a small number of medicines, and, moreover, the effect derived in a number of cases is weak.

For the success of treatment, meanwhile, medicine must in general have the possibility of regulating the action time of the drug that is in the patient's organism. Some should be withdrawn more swiftly, others, on the contrary, retained longer. Heretofore the doctor had no such possibility.

Hence a new idea was born, the idea of controlling therapeutic substances inside the patient's organism.

Medicine is usually introduced either directly into the patient's blood or into the muscles or stomach, from which it afterward enters the blood. At the same time it always remains extraneous to the organism which naturally tends to get rid of this surplus substance. The idea of Soviet chemists consisted in building a medicine in a giant molecule of a blood substitute and in this way make it for a time like a component part of the organism itself.

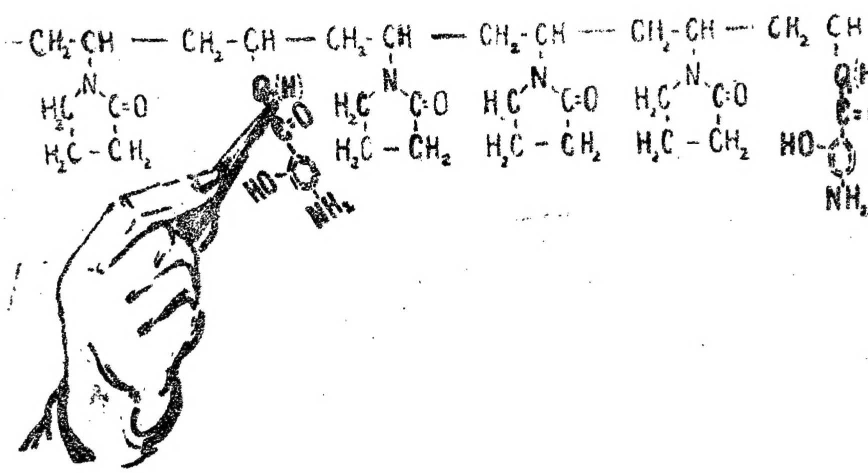
Built-on Molecules

These same polymers came to the rescue, substances with huge molecules which Ushakov had been engaged for many years in studying. For a chemist to lengthen or shorten a molecule in such a polymer, for example, as the artificial blood substitute PVP, is not essentially very difficult. The magnitude of the molecule of the administered substance is, however, not at all a matter of in-

difference for the organism.

It is known that the longer the molecule of any medicinal preparation, the longer the time it is retained in the human body. Such molecules circulate for a long time in the blood or "get clogged" in the liver until they finally disintegrate into simpler compounds. It is just this quality, the magnitude of the molecules which chemists have built artificially, that, as has already been said, makes the synthetic blood substitute so valuable.

The PVP molecule can be pictured in the form of a long chain. Buch can such a molecular chain not be used in order to build into, "attach to," it the molecules of that medicine whose action in the organism we wish to prolong? To attach to the chain, for example, of a blood substitute, the molecule of penicillin.



"in my opinion, it can be done," says the professor, "and we should do it." Why if the doctor administers such a synthetic preparation to the blood of a patient in need of penicillin, he will get a medicine that will have a therapeutic effect in as much time as the physician requires.

"At the same time, blood substitutes can be selected with molecules of varied length, and consequently, the duration of their 'life' inside the organism (and with them also "attached" medicines) can be regulated with great accuracy."

About two years ago scientists set about the

practical realization of this idea at one of the laboratories of the Institute of High-molecular-weight Compounds, Academy of Sciences, USSR, Leningrad.

First of all an appropriate blood substitute, the base of the future medicine, had to be chosen. It had to be a substance to whose molecular chain the molecules of medicine might be attached with comparative ease. PVP proved of little value for this purpose. To "hook-on" side chains to it is not convenient.

The structure of the blood substitute had to be revised. Between the molecular links of the PVP chain, Ushakov "builds in" additional links -- vinyl alcohol. A test was made to determine if the preparation had at the same time lost the quality of blood substitute. No! On the other hand, it was no longer difficult to attach penicillin and other medicines to vinyl alcohol: the attachment is made by means of primary valence bonds. Depending on the nature of the attached medicine, other compounds -- crotonic and maleic acids and others -- are employed in the capacity of additional links.

This method differs in principle from all known means of deriving medicines and medicinal preparations. In consequence of building medicinal substances onto molecules of the blood substitute, completely new chemical substances are formed, medicinal preparations such as medicine has not yet known.

In creating these new substances, however, the chemists must consider many aspects. The molecules of the medicine itself have several active radicals. Which of them is to be attached to the blood substitute's molecular chain? Apparently, not every radical is good for this purpose. Investigations have to be made to show just how this or that medicine should be attached, so as not to lose at the same time its therapeutic properties.

The proposal to include a medicine in the chemical structure of the polymer-blood substitute was considered by specialists of the Leningrad Blood Transfusion Institute, Institute of Experimental Medicine, City Department of Health. The Science Council of the Ministry of Health USSR also gave its positive conclusion.

But which medicines is it important to synthesize by the new method in the first place? Specialists from various fields of medicine address the most varied requests to chemists.

We have already spoken of penicillin and PASK. Just as important is the request of doctors who treat heart and blood vessel diseases. Clots of blood, thrombi, often form in the vessels of cardiac patients. To prevent their

appearance, patients are administered a medicine, dicoumarin, which reduces the danger of the formation of thrombi. But in this case as with PASK, the medicine has to be applied very frequently as it rapidly departs from the organism. The doctors want to have a dicoumarin which will remain in the blood stream as long as possible.

Surgeons request that novocain, an anesthetic substance, be attached to a blood substitute. Then, when transfusing blood to the patient under operation, they can at the same time diminish the painful sensations.

But there is still another large problem of medicine, the successful solution of which depends on synthetic chemistry.

"Watch Your Arteries"

Under such a title an article appeared recently in an American magazine and immediately attracted the attention of specialists. Doctors, of course, the reader will say. No, chemists. And the magazine which printed the article was a scientific chemical publication. But why had the chemists invaded medicine.

There is such a disease called atherosclerosis. It is manifested in that a fatty substance, cholesterol, is deposited on the internal walls of the sick person's blood vessels. Because of this the vessels become fragile and brittle.

It has, however, long since been observed that for some reason atherosclerosis very rarely affects inhabitants of Italy, Greece and... the shore of the Arctic ocean. It may appear that the living conditions of Mediterranean peoples and inhabitants of the Far North are completely different, or that only a coincidence is involved.

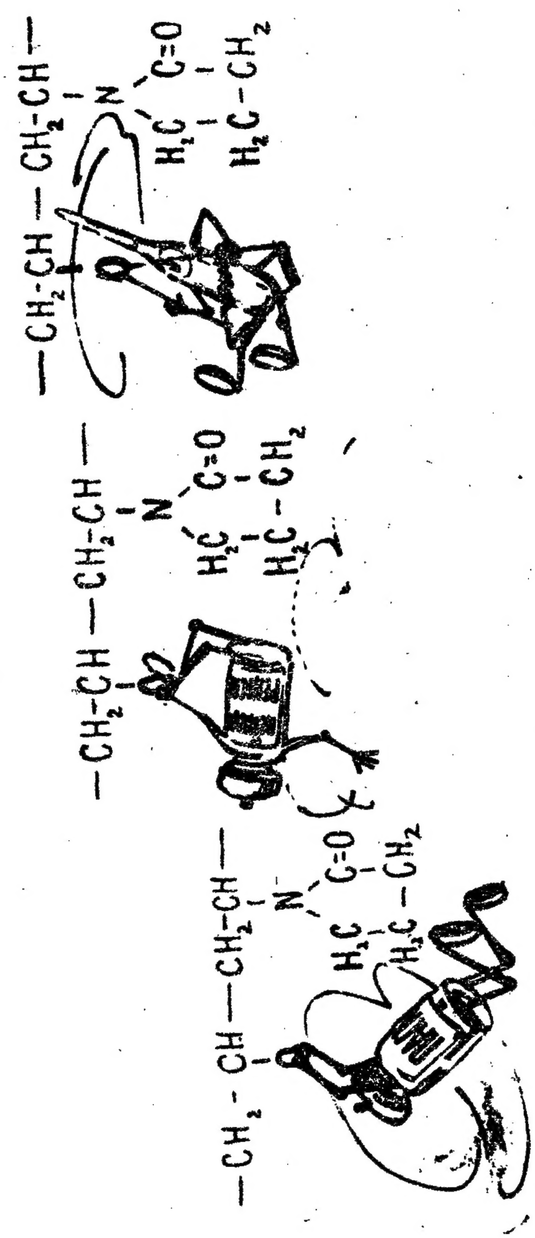
But careful investigations have shown that a common cause lies behind the identical nonsusceptibility to atherosclerosis of these peoples. The point is that the Greek and Italians use olive oil and the Eskimos use fish fat as the chief nutritional fat. And olive oil and fish fat are, as chemists say, "unsaturated" fats. If they are consumed constantly, the quantity of cholesterol in the blood of a person is sharply reduced, and consequently, the danger of atherosclerosis is abated.

The greater part of the fat is absorbed in the intestine directly from the alimentary canals and in the form of a thin emulsion gets into the blood. The unsaturated fats at the same time enter into some kind of interaction with cholinesterol, that is as yet not fully known, and thereby seemingly "fixate" it.

It was precisely this complex interaction between saturated and nonsaturated fats which has become an object of research among scientists of various countries, that the article in the chemical magazine was also devoted to. Whether or not the nonsaturated fats can extract cholesterol from deposits that have already formed on the walls of vessels, i.e. cannot only prevent but also cure atherosclerosis by this means, is still unknown, that the beneficial effect of such oils has undoubtedly been recorded by many scientists. In America a factory has even been built that manufactures from sunflower oil a special nonsaturated fat, "glenoil."

There is, however, one circumstance that seriously hampers the use of nonsaturated fats for the purposes indicated. The point is that on entering the blood, this substance very rapidly precipitates into "fatty deposits" in muscular and connective tissue, whereas the saturated fats, on the contrary, are retained in the blood stream for a fairly long time. Right here we approach a new proposal by which Prof. Ushakov substantially adds to the work of foreign chemists.

The Soviet scientist proposed that the nonsaturated fats, more precisely their fatty acids, be connected by chemical bond with blood substitutes just as it is proposed to do with medicines. Such "long-living" nonsaturated fats can run through the blood stream many times, "washing off" and carrying out from the organism particles of cholesterol. The treatment of atherosclerosis by preparations of "long-living" nonsaturated fats will, of course, require more detailed investigations of pharmocologists and physicians. But the Leningrad chemists begin work this year on the creation of new fatty preparations, transmitting to medicine a powerful weapon in the struggle against atherosclerosis. Other blood substitutes, in addition to PVP, can be used as medicine carriers.



Prof. Ushakov believes that the new method of creating medicinal preparations, having medicines built right in the molecule of organic substances introduced into the patient's organism, will open immense possibilities for doctors. The chemist already envisages medicines where in the giant molecule of a blood substitute metals like mercury, silver, lead and lithium, having a killing action on microbes, have been successfully introduced. In the very same manner, various antibiotics and anti-cancer preparations can be retained in the organism.

The Leningrad chemists, in creating a medicine which is new in principle, must solve a highly important problem, the very raising of which has become possible on account of the achievements of modern chemistry, and the chemistry of polymers, in the first place.

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